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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/966,768	09/28/2001	Derek Van Der Kooy	Bereskin & Parr	6817

110 7590 11/17/2004

DANN, DORFMAN, HERRELL & SKILLMAN
1601 MARKET STREET
SUITE 2400
PHILADELPHIA, PA 19103-2307

EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
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1636

DATE MAILED: 11/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/966,768

Applicant(s)

VAN DER KOOY ET AL.

Examiner

Daniel M Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-11, 13-17, 20-22, 25-27, 29-38, 41, 42 and 47-49 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-3, 7-11, 13-17, 20-22, 25-27, 29, 30, 32-38, 41, 42 and 47-49 is/are allowed.
- 6) ☒ Claim(s) 4-6 and 31 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Office Action is a reply to the Paper filed 26 October 2004 in reply to the Final Office Action mailed 30 August 2004. Claims 1-11, 13-17, 20-22, 25-38, 41-43 and 47-49 were considered in the 30 August Office Action. Claims 28 and 43 were canceled in the 26 October Paper. Claims 1-11, 13-17, 20-22, 25-27, 29-38, 41, 42 and 47-49 are pending and under consideration.

Finality of the previous Office Action is hereby withdrawn in view of the new grounds for rejection set forth below.

Response to Amendment

Rejection of claims 28 and 43 is rendered moot by cancellation of the claims.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Although the claim was previously indicated as allowable, upon further consideration, it is clear that the claim lacks adequate descriptive support. The claim was previously rejected as lacking adequate written description in the Office Action mailed 28 August 2002. Although the rejection was withdrawn in the Office Action mailed 23 May 2003 in view of Applicant's arguments, upon careful review of the originally filed disclosure and arguments of record it is apparent that the disclosure does not provide adequate descriptive support for the claim.

The *prima facie* case set forth in the 28 August Office Action reads essentially as follows:

Claim 31 is drawn to a method of producing a preselected cell type derived from a primitive neural stem cell. Given their broadest reasonable interpretation, the claims encompass a method of producing any cell type by culturing cells under differentiating conditions that promote formation of the cell type. However, the disclosure only provides description of the claimed method as it would be applied to producing or screening for differentiation toward a neural cell phenotype. Given that the methods disclosed could not be used to determine, for example, differentiation toward muscle cell or endothelial cell phenotypes, the Application does not provide adequate written description to support the full scope of the claim. One of ordinary skill in the art would therefore not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate with its scope.

In the reply filed 6 March 2003, Applicant argues that the specification teaches the *in vivo* differentiation of primitive neural stem cell-derived cells into neural and non-neural cell types, and that the application describes that it is generally known that embryonic stem cells differentiate into neural or epidermal cells. These arguments have been fully considered but are

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not persuasive. The instant claim 31 is explicitly limited to producing a preselected cell type by culturing the cells under differentiating conditions. Although the teachings cited in the specification suggest that the primitive neural stem cells possess the potential to differentiate into non-neuronal stem cells *in vivo*, there is no description of any *in vitro* “differentiating conditions” that would lead to the expression of a non-neuronal phenotype. Furthermore, there is no description of *in vitro* conditions that would produce the broad scope of all preselected neuronal cell types (*e.g.*, serotonergic neurons *versus* dopaminergic neurons). Adequate written description of a method for producing a preselected cell type by culturing the cell under differentiating conditions requires a description of the differentiating conditions used in the method. The absence of such a description is not remedied by describing a different method of obtaining a selected cell type (*i.e.*, *in vivo* differentiation of primitive neural stem cell-derived cells).

Applicant further argues that conditions for ES cell differentiation into multiple cell types is also described in the application by reference to Yamashita *et al.* (2000) *Nature* 408: 92-96. Yamashita *et al.* teaches a method by which Flk1⁺ cells derived from embryonic stem cells can differentiate into endothelial and mural cells. However, Yamashita *et al.* does not describe differentiating conditions capable of promoting formation of any preselected cell type from primitive neural stem cells. In fact, there is no evidence that the Flk1⁺ cells of Yamashita *et al.* are the same as the instant primitive stem cells, or that the differentiating conditions described by Yamashita *et al.* would produce endothelial and mural cells from primitive neural stem cells. Thus, the teachings of Yamashita *et al.* do not adequately describe differentiating conditions capable of producing any selected cell type from a primitive neural stem cell.

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For these reasons, the disclosure fails to provide adequate descriptive support for the subject matter of claim 31.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: Claim 31 is directed to a method of producing a preselected cell type derived from the primitive neural stem cell of the invention by culturing the cells in LIF under differentiating conditions. The claim thus embraces a method of producing any desired cell type from the primitive neural stem cells by exposing the cells to the appropriate differentiating conditions in culture. As practicing the claimed invention to produce any given cell type requires that the cells be exposed to the appropriate differentiating conditions for that cell type, the enabling disclosure must teach the skilled artisan which differentiation

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conditions can be used to produce any given preselected cell type such that the invention can be practiced commensurate its full scope.

State of the prior art and level of predictability in the art: The art does not teach the primitive neural stem cells of the present invention or general methods of providing any preselected cell type from a partially differentiated ES cell. However, the art recognizes that, although cells having phenotypic characteristics of a variety of cell types have been produced from ES cells *in vitro* a recent review of the stem cell art published at approximately the time the instant application was filed teaches, “[i]t is not possible to explain *how* the directed differentiation occurs...No one knows how or when gene expression is changed, what signal-transduction systems are triggered, or what cell-cell interactions must occur to convert undifferentiated ES cells into precursor cells and, finally, into differentiated cells that look and function like their *in vivo* counterparts” (*Stem Cells: Scientific Progress and Future Research Directions*. “Chapter 2. The Embryonic Stem Cell”, Department of Health and Human Services. June 2001. <http://stemcells.nih.gov/info/scireport/chapter1.asp> (hereinafter, *Stem Cells*), bridging pages 7-8). Thus, the art teaches that although ES cells are pluripotent, the *in vitro* production of any given cell type from an ES cell requires proper manipulation of culture conditions. Furthermore, the art teaches that, at the time of filing, it was not possible to predict what manipulations would be required to produce any given cell type based on experience obtained producing other cell types from ES cells.

Amount of direction provided by the inventor and existence of working examples: The present disclosure teaches a method of producing primitive neural stem cells by culturing embryonic stem cells at low density in a serum-free and feeder-layer free media comprising

leukemia inhibitory factor. In Example 7, the disclosure teaches that when the primitive neural stem cells are introduced into embryos the cells contribute to a variety of embryonic tissues. However, the specification is silent with regard to which culture conditions should be used to produce any given cell type from the primitive neural stem cells of the invention.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to practice the instant claim without engaging in undue experimentation. The art teaches, “No one knows how or when gene expression is changed, what signal-transduction systems are triggered, or what cell-cell interactions must occur to convert undifferentiated ES cells into precursor cells and, finally, into differentiated cells that look and function like their *in vivo* counterparts” (*supra*). Therefore, providing differentiation conditions capable of producing any preselected cell type from a primitive neural stem cell is clearly not considered routine in the art. In spite of this, the instant application provides no specific guidance as to how any particular preselected cell type might be produced from the primitive neural stem cells, let alone the wide variety of cell types within the scope of the claim. Given the art recognized unpredictability of obtaining preselected cell types from ES cells in culture and the absence of specific guidance in the instant specification, practicing the invention if claim 31 would require that the skilled artisan engage in empirical experimentation to determine which differentiation conditions should be used to produce each preselected cell type. As this would clearly require undue experimentation the disclosure is not adequately enabling for the claimed subject matter. Therefore, claim 31 is properly rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4-6 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in reciting "said cell density is greater than 0 cells/ μ l to 50 [20 or 10] cells/ μ l." The limitation can be interpreted as requiring that the cell density fall within the range of greater than 0 cells/ μ l to less than or equal 50 cells/ μ l, or can be understood to mean that the a cell density is greater than 0 cells/ μ l to greater than 50 cells/ μ l. Given that there are alternative ways of interpreting the range, the metes and bounds of the claims are unclear.

Allowable Subject Matter

Claims 1-3, 7-11, 13-17, 20-22, 25-27, 29, 30, 32-38, 41, 42 and 47-49 are allowed.

Claims 4-6 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779.

The examiner can normally be reached on Monday through Thursday 6:30-5:00.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel M Sullivan, Ph.D.
Examiner
Art Unit 1636

Anne-Marie Falk
ANNE-MARIE FALK, PH.D.
PRIMARY EXAMINER